

Research Article :

Clinical profile and liver function in Dengue

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Abstract:

Unusual clinical manifestations of dengue fever have become more common in the last few years. Although the liver is not a major target organ, hepatic dysfunction is a well-recognized feature, often characterized by acute hepatitis, with pain in the right hypochondrium, hepatomegaly, jaundice and raised aminotransferase levels. Of late there have been multiple reports of fulminant hepatitis in children with dengue fever. Hence the following prospective observational study in 100 consecutive patients with dengue fever was conducted to find out the profile of liver involvement in children with dengue viral infection. **Study Setting:** The present study was conducted at Sri Venketeswara Ram Narayan Ruia Government General Hospital, Tirupati. **Inclusion criteria:** All NS1 Ag positive or dengue Ig M positive cases in the age group of 6 months to 12 years irrespective of sex admitted in Department of Pediatrics, Sri Venketeswara Ram Narayan Ruia Government General Hospital, Tirupati. **Exclusion criteria:** Children with pre-existing liver disease and children with other infections causing hepatitis like Malaria, Hepatitis B, Enteric fever and Leptospirosis. **Study design:** Hospital based prospective observational study. All children included in the study were investigated for complete blood count, NS1 antigen, serum dengue IgM or IgG antibodies. Liver function tests namely serum total bilirubin, total protein, serum albumin, aspartate transaminase, alanine transaminase, alkaline phosphatase, prothrombin time, international normalized ratio. Other tests like activated partial thromboplastin time, bleeding time, clotting time. **Results:** Liver function tests AST, ALT and Alk phosphatase, bilirubin were deranged in children with severe dengue and

dengue with warning signs compared to dengue without warning signs. Total bilirubin, AST, ALT and alkaline phosphatase derangements were highly significant with p-value 0.001. The mean prothrombin time (PT), mean activated partial thromboplastin time (APTT), and international normalized ratio were significantly higher in severe dengue compared to dengue with warning signs and dengue without warning signs. **Conclusions:** We have found in our study that deranged liver functions are an important feature in patients with dengue infection. In children with dengue fever without warning signs 13 children had AST elevation 1-3 times the normal value and 8 children had AST elevation 4-10 times the normal value. In children with dengue with warning signs 19 children had AST elevation 1-3 times the normal and 35 children had AST elevation 4-10 times the normal value. In children with severe dengue 9 children had AST elevation 4-10 times the normal value and 16 children had AST value above 10 times the normal value.

Keywords:

Dengue, aminotransferases, liver function tests, hepatitis

Introduction:

Dengue is a mosquito borne infection found in tropical and sub-tropical regions around the world. In recent years, transmission has increased predominantly in urban areas and has become a major international public health concern [1].

The incidence of Dengue has grown dramatically around the world in recent decades. Over 25 billion people (40% of the world's population) are now at risk from Dengue. WHO

currently estimates, there may be 50-100 million dengue infections world-wide every year [1].

Unusual clinical manifestations of dengue fever have become more common in the last few years. Although the liver is not a major target organ, hepatic dysfunction is a well-recognized feature, often characterized by acute hepatitis, with pain in the right hypochondrium, hepatomegaly, jaundice and raised aminotransferase levels [2-19].

Liver dysfunction as a result of dengue infection can be a direct viral effect on liver cells or an adverse consequence of dysregulated host immune response against the virus [6]. Dengue fever is known to involve multiple systems sometimes resulting in multi organ dysfunction. Liver involvement is known to occur and of late there have been multiple reports of fulminant hepatitis in children with dengue fever. Hence the following prospective observational study in 100 consecutive patients with dengue fever was conducted to find out the profile of liver involvement in children with dengue viral infection.

Material and methods

Study Setting:

The present study was conducted at Sri Venkateswara Ram Narayan Ruia Government General Hospital, Tirupati.

Inclusion criteria:

All NS1 Ag positive or dengue Ig M positive cases in the age group of 6 months to 12 years irrespective of sex admitted in Department of Pediatrics, Sri Venkateswara Ram Narayan Ruia Government General Hospital, Tirupati.

Exclusion criteria:

Children with pre-existing liver disease and children with other infections causing hepatitis like Malaria, Hepatitis B, Enteric fever and Leptospirosis.

Study design:

Hospital based prospective observational study.

All children included in the study were investigated for complete blood count, NS1 antigen, serum dengue IgM or IgG antibodies. Liver function tests namely serum total bilirubin, total protein, serum albumin, aspartate transaminase, alanine transaminase, alkaline phosphatase, prothrombin time, international normalized ratio. Other tests like activated partial thromboplastin time, bleeding time, clotting time

Results:

56% were males and 44 % were females. The male: female sex ratio was 1.27:1.8 out of 10 children whose age is less than one year presented with severe dengue. Remaining two children presented with warning signs. In the age group of one to five years. 9 children presented without warning signs, 23 children are with warning signs and 12 had severe dengue. In children between 6 to 12 years 12 children had dengue without warning signs, 29 children presented with warning signs and 5 children with severe Dengue. Liver size does not correlate with disease severity or abnormal liver function tests, presence of an enlarged liver is observed more frequently in severe dengue and dengue with warning signs compared to dengue without warning signs with a p-value of 0.026. The hepatic involvement may be due to direct infection of the dengue virus or due to immune mediated hepatocyte injury or various other mechanisms as mentioned earlier. Pain abdomen in dengue fever can be due to mesenteric lymphadenitis, hepatic enlargement or bowel wall ischemia secondary to shock. Pain abdomen was more common in children with severe dengue as compared to children with dengue with warning signs. Pain abdomen was seen in 50% of our cases is comparable to earlier studies which had an incidence of 40 to 50% [22,23].

Vomiting in dengue fever may be due to

hepatic involvement, mesenteric adenitis or bowel wall ischemia. Vomiting was present in 55% of the cases and was significantly more common in children with severe dengue and dengue with warning signs as compared to dengue without warning signs with a p-value of 0.001. Overall incidence of vomiting is 55% which is comparable to earlier studies.

Rash was seen in 52% of the cases which is comparable to earlier studies by Saba Ahmed et al[19]. Incidence is more in children with severe dengue compared to children with dengue with warning signs and dengue without warning signs with a p-value of 0.001. Edema was seen in 56% of the cases. In present study 22.2% of children with dengue with warning signs had bleeding manifestations and 76% of children with severe dengue had bleeding manifestations. Incidence of petechiae increased with severity of disease with a p-value of 0.001. In present study there was no relationship in incidence of lymphadenopathy headache, vomiting and splenomegaly with the severity of disease

Table 1: Age and Gender distribution of Patients with Dengue Fever

| Age (Years) | Dengue without warning signs(n=21) | Dengue with warning signs(n=54) | Severe Dengue (n=25) | Percentage |
|-------------|------------------------------------|---------------------------------|----------------------|------------|
| < 1 | 0(0%) | 2(3.7%) | 8(32.0%) | 10(10.0%) |
| 1-5 | 9(42.8%) | 23(42.5%) | 12(48.0%) | 44(44.0%) |
| 6-12 | 12(58.2%) | 29(53.7%) | 5(20.0%) | 46(46.0%) |
| Sex | | | | |
| Male | 9(42.8%) | 31(57.4%) | 16(64.0%) | 56(56.0%) |
| Female | 12(57.2%) | 23(42.6%) | 9(36.0%) | 44(44.0%) |

Table 2: Laboratory Parameters

| Measurement | Mean | Range Min | Range Max |
|-----------------|-------|-----------|-----------|
| Hb | 8.91 | 4.0 | 13.0 |
| Hct | 33.46 | 18.0 | 52.0 |
| Platelet | 46654 | 10000 | 400000 |
| Total bilirubin | 1.082 | 0.3 | 2.3 |
| Sr. Proteins | 6.6 | 5.5 | 7.8 |
| Albumin | 4.723 | 3.5 | 5.5 |
| AST | 231.3 | 46 | 922 |
| ALT | 201.1 | 42.0 | 766.0 |
| ALP | 145.1 | 49.0 | 290.0 |
| PT | 16.06 | 13.0 | 38.0 |
| APTT | 32.73 | 30.2 | 52.0 |
| INR | 1.429 | 1.04 | 4.4 |
| BT | 4.84 | 1.1 | 9.3 |
| CT | 4.409 | 1.0 | 8.5 |

The mean haemoglobin, haematocrit and platelet counts at presentation were 8.91 g/dl, 33.46 and 46654 respectively. The mean total bilirubin, albumin, AST, ALT, Alk phosphatase level were 1.082, 4.723g/dl, 231.3 U/L, 201.1 U/L and 145.1 U/L respectively. The mean PT, aPTT, INR, BT and CT were 16.06, 32.73s, 1.429, 4.84 mins and 4.409 mins respectively.

Table 3: Comparison of Liver Function Test Derangements in Patients with Dengue Fever

| Measurement | Dengue without warning signs | | Dengue with warning signs | | Severe Dengue | | F value | P value |
|-----------------|------------------------------|--------|---------------------------|--------|---------------|--------|---------|---------|
| | Mean | SD | Mean | SD | Mean | SD | | |
| Total bilirubin | 0.661 | 0.162 | 1.17 | 0.445 | 1.228 | 0.22 | 18.648 | 0.001 |
| Sr. Proteins | 6.585 | 0.568 | 6.707 | 0.486 | 6.712 | 0.541 | 0.469 | 0.627 |
| Albumin | 4.86 | 0.521 | 4.722 | 0.452 | 4.608 | 0.382 | 1.802 | 0.170 |
| AST | 108.19 | 29.872 | 168.05 | 83.09 | 471.36 | 223.08 | 60.696 | 0.001 |
| ALT | 96.23 | 26.105 | 149.4 | 74.780 | 400.92 | 174.17 | 64.45 | 0.001 |
| Alk.phosphatase | 119.904 | 24.180 | 132.85 | 33.411 | 192.76 | 47.34 | 30.4 | 0.001 |

Liver function tests AST, ALT and Alk phosphatase, bilirubin were deranged in children with severe dengue and dengue with warning signs compared to dengue without warning signs. Total bilirubin, AST, ALT and alkaline phosphatase derangements were highly significant with p-value 0.001. Enzymes are elevated significantly in severe dengue compared to dengue with and without warning signs.

Table 4: Comparison of Coagulation Test Derangements in Patients with Dengue Fever

| Measurement | DWWS | | DWS | | Severe Dengue | | F value | P value |
|-------------|-------|-------|-------|-------|---------------|------|---------|---------|
| | Mean | SD | Mean | SD | Mean | SD | | |
| PT | 15.1 | 1.427 | 14.9 | 1.21 | 19.36 | 7.58 | 11.744 | 0.001 |
| APTT | 32.07 | 1.00 | 32.17 | 1.077 | 34.48 | 6.41 | 4.677 | 0.012 |
| INR | 1.30 | - | 1.27 | - | 1.86 | - | - | - |

The mean prothrombin time (PT), mean activated partial thromboplastin time (APTT), and international normalized ratio were significantly higher in severe dengue compared to dengue with warning signs and dengue without warning signs.

Discussion:

In present study the mean age of presentation in children with severe dengue is 3.31 years. Mean age of presentation in children with warning signs is 5.85 years and mean age of presentation in children without warning signs is 6.42 years. Overall mean age of presentation is 5.6 years. It is comparable with studies done by Cam et al [20], and Pancharoen et al [21]. Edema was seen in 56% of the cases. Other studies have showed an incidence of 40 to 45%. Incidence of edema increased with severity of disease with a p-value of 0.001. Icterus was seen in 2 cases. It was seen only in children with severe dengue. Bleeding manifestations like petechiae are seen in 31% of children. Incidence of bleeding manifestations is low in present study compared to other studies which had an incidence of 35-66%.

In the present study, the mean hemoglobin at presentation was 8.91 g/dl. Minimum hemoglobin in our study is 4 g/dl and maximum value of haemoglobin is 13 g/dl. In other studies, it ranged from 10.8 g/dl to 13.7 g/dl. In our study the mean haematocrit is 33.46. Minimum haematocrit value is 18 and maximum value of haematocrit is 52. The mean value of platelet in present study is 46,654 and minimum value of platelet count is 10,000 and maximum value of platelet count is 4,00,000. In this study the incidence of severe dengue is 25% and incidence of dengue with warning signs is 54, both of them combined it accounts

to 79%. The high incidence in present study might be which attributed to the fact that the study was done in tertiary care referral hospital

We have found in our study that deranged liver functions are an important feature in patients with dengue infection. In children with dengue fever without warning signs 13 children had AST elevation 1-3 times the normal value and 8 children had AST elevation 4 -10 times the normal value. In children with dengue with warning signs 19 children had AST elevation 1-3 times the normal and 35 children had AST elevation 4-10 times the normal value. In children with severe dengue 9 children had AST elevation 4-10 times the normal value and 16 children had AST value above 10 times the normal value.

AST elevation increased with severity of disease with a p-value of 0.001. The mean value of AST in children with dengue without warning signs is 108.19. The mean value of AST in children with dengue with warning signs is 168.05. The mean value of AST in severe dengue is 471.36.

In children with dengue fever without warning signs 18 children had ALT elevation 1-3 times the normal value and 3 children had ALT elevation 4--10 times the normal value. In children with dengue fever with warning signs 18 children had ALT elevation 1-3 times the normal value and 3 children had ALT elevation 4-10 times the normal value.

Elevation in ALT is directly proportional to severity of disease with a p-value of 0.001. The mean value in ALT children with dengue without

warning signs is 96.23, in children with dengue with warning signs the mean value of ALT is 149.4, in children with severe dengue the mean value of ALT is 400.92.

Alkaline phosphatase values increased with severity of disease with a p-value of 0.001. The mean value of alkaline phosphatase in children with dengue without warning signs is 119.904, in children with dengue with warning signs the mean value of alkaline phosphatase is 132.85, in children with severe dengue the mean value of alkaline phosphatase is 192.76.

The mean total bilirubin level in the present study was 1.082 gm/dl. Other studies reported mean total bilirubin levels of 0.8 g/dl to 0.93 g/dl. In children with dengue without warning signs mean total bilirubin is 0.661. In children with dengue with warning signs mean total bilirubin is 1.17. In children with severe dengue mean total bilirubin is 1.228. Bilirubin elevation is more in children with severe dengue compared to dengue with warning signs and dengue without warning signs with a p-value of 0.001.

In the present study the mean value of serum proteins is 6.6. In children with severe dengue the mean value of serum proteins is 6.712. In children with dengue with warning signs mean value of serum proteins is 6.707. In children with dengue without warning signs mean value of serum proteins is 6.585. There is no variation in the value of serum proteins with severity of dengue with a p-value of 0.627. The mean albumin level was 4.723 g/dl.

Table 5: Liver Function Tests Comparison Studies

| Tests | ChinnaRS et al ⁴ | Prakash et al ⁶ | Wong M et al ⁹ | Present study |
|----------------|-----------------------------|----------------------------|---------------------------|---------------|
| Totalbilirubin | 0.93 mg/dl | 0.8 mg/dl | 1.62 mg/dl | 1.082 |
| Sr. Albumin | 3.2 g/dl | | 3.89 g/dl | 4.723g/dl |
| AST | 353.7 U/L | 174 U/L | 163.18 U/L | 231.31 U/L |
| ALT | 218.6 U/L | 88.5 | 144.58 U/L | 201.14U/L |
| ALP | 135.2 U/L | 80 U/L | 70.08 U/L | 145.1 U/L |

This table compares the various liver function tests in three other studies with our study. The data in the present study is comparable with earlier study done by Chinnaet al[4] except for normal bilirubin level and normal protein and albumin level.

All the liver function tests (Total bilirubin, AST, ALT and Alk phosphatase) were higher in children with severe dengue compared to dengue fever with warning signs and dengue fever without warning signs with P value <0.05 for all the above mentioned parameters which is comparable to earlier studies.

The mean AST and ALT levels were 231.31 and 201.14 U/L respectively. The mean value of AST was significantly higher than the mean values of ALT which is comparable to other studies. This differs from the pattern in viral hepatitis, the exact cause of which is uncertain. It has been suggested that it may be due to excess release of AST from damaged monocytes during dengue infection. Mean ALP value in our study is 145.1 and minimum ALP value in our study is 49 and maximum ALP value in our study is 290. Liver involvement occurred through an inflammatory process in the parenchyma provoked directly or indirectly by the virus, reducing the diameter of the lumen of the biliary canaliculus, causing obstruction and leading to bilirubinemia, jaundice and elevated alkaline phosphatase levels as reported in earlier studies which is in accordance with our study.

The mean PT and APTT levels were 16.06 and 32.73 and mean international normalized ratio is 1.42. The mean prothrombin time (PT), mean activated partial thromboplastin time (APTT) were significantly higher in the severe dengue compared to dengue with warning signs and dengue without warning signs. Derangements in our study are either due to more virulent strain of dengue infection or virus is more hepatotoxic. Therefore further studies are required to highlight the possible hepatotropic nature of this virus as well as virulence and type of virus.

In our study, the mortality rate was 3% and all the 3 patients had low platelet count, high haematocrit, elevated alkaline phosphatase and deranged liver enzymes, elevated prothrombin time and INR.

Limitations of present study:

1.Small Sample Size
2.Repetition of liver function test not done.
3.There is no follow up of cases included in the study.

Recommendations for further study:

The present study shows significant association between abnormality of liver function tests and severity of dengue fever. Although it shows statistically significant association between liver function tests and severity of dengue, it is not enough to confirm the association. It appears that liver function test in each population varies with multifactorial inter-relationships. Larger control studies are desirable.

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